Hot tip: Target inflammation to ease obesity ills

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(AP) -- What if you could be fat but avoid heart disease or diabetes? Scientists trying to break the fat-and-disease link increasingly say inflammation is the key.

In the quest to prove it, a major study is under way testing whether an anti-inflammatory drug - an old, cheap cousin of aspirin - can fight the Type 2 diabetes spurred by obesity.

And intriguing new research illustrates how those yellow globs of fat lurking under the skin are more than a storage site for extra calories. They're a toxic neighborhood where inflammation appears to be born.

Diabetes and heart disease usually tag along with extra pounds, a huge risk for the two-thirds of Americans who are overweight or obese. What isn't clear is what sets off the cascade of damage that ends in those illnesses. After all, there are examples of obese people who somehow stay metabolically fit - no high blood pressure or high blood sugar or high cholesterol.

"If fat cells functioned perfectly, you could be as obese as you want and not have heart disease," says Dr. Carey Lumeng of the University of Michigan. "It's something we don't understand, why some people are more susceptible and others are not so susceptible."

Solving that mystery could point to more targeted treatments for obesity's threats than today's effective but hard-to-follow advice to lose

weight. The chief suspect: Inflammation that the immune system normally uses to fight infection runs amok with weight gain - simmering inside fat tissue before spreading to harm blood vessels and spur insulin resistance.

"We all think it's bad, and we know a lot of people with really bad inflammation die sooner," says Dr. Myrlene Staten of the National Institutes of Health's diabetes division.

Dr. Steven Shoelson at the Harvard-affiliated Joslin Diabetes Center noted reports from 150 years ago that one of the oldest anti-inflammatories around - salsalate, from the aspirin family - could lower blood sugar. Less harsh on the stomach than aspirin, generic salsalate is used today for arthritis, and Shoelson discovered that it inhibits what he calls a master switch in inflammation regulation.

"We put those pieces together and sure enough, it does work," says Shoelson.

Pilot trials found short-term use of salsalate, added to regular diabetes medication, helped poorly controlled Type 2 diabetics lower their blood sugar substantially. Fasting glucose levels dropped from about an average of 150 down to 110, Schoelson says.

Now an NIH-funded study is recruiting several hundred Type 2 diabetics at 21 medical centers around the country to take the drug or a dummy pill for a year, to track long-term effects.

But what sparks that inflammation in the first place? Other researchers are hot on the trail of immune cells called macrophages that cluster inside fat tissue.

In a novel study, Dr. Preeti Kishore of Albert Einstein College of

Medicine took 30 somewhat overweight but healthy volunteers and infused free fatty acids, a type of fat molecule, directly into their blood. She was mimicking what happens in the obese, when these fatty acids spill out from stored fat and continually flow through the body.

The results were startling: For five hours, the volunteers' bodies quit responding effectively to insulin. They also experienced a surge in a protein called PAI-1 (pronounced Pie-one) that sets off a chain reaction linked to heart disease-causing blood clots and diabetes. When Kishore took samples of the volunteers' fat tissue, she found the macrophages start producing more PAI-1 as they are bathed in the fatty acids.

The more pounds you put on, the bigger fat cells called adipocytes become until they release fatty acids and eventually die. The theory is that macrophages come in to clean up the dead cells but are hijacked to produce inflammation-causing chemicals - signals that also spur further adipocyte dysfunction. Kishore's work suggests fat tissue primes macrophages to be switched on by a boost in fatty acids, starting the inflammation cycle.

"What's really exciting to us, is trying to understand these mechanisms can essentially help us to target therapies more effectively in the future," says Kishore, whose research was published last week in the journal Science Translational Medicine.

She points to Shoelson's study of salsalate - which blocks a related protein found in macrophages and other immune cells - as a first step.

"Four to five years ago, no one thought fat tissue matters for this stuff," adds Michigan's Lumeng, who studies the macrophage link. "There clearly are going to be anti-inflammatory therapies for diabetes coming out of the pipeline."